Section II (Remarks)

A. Summary of Amendment to the Claims

By the present Amendment, claim 1 has been amended. No new matter within the meaning of 35 U.S.C. §132(a) has been introduced by the foregoing amendments.

Specifically, claim 1 has been amended to add the language "…and wherein the rat develops active HIV infection after exposure to HIV, with expression of antibodies or viral antigen in sera thereof." Such language is fully supported in the specification. In particular, on page 20, lines 21-22 the specification provides "…active HIV-1 infection of a huCD4 transgenic rat…should be possible." In Example 11, following infection of hCD4 transgenic rats with HIV, "[t]he presence of HIV-1 antibodies and viral antigen…in the sera can then be analyzed..." As provided in paragraph 8 of the Declaration of Dr. Joseph Bryant, filed with the USPTO November 20, 2008, "[t]he hCD4 transgenic rat was infected with HIV-1 according to the specific disclosure of Example 11 of the application…" As such, a hCD4 rat has been generated according to the teachings of the invention and such rat has been infected with HIV and tested for such infection through observation of HIV-1 antibodies and viral antigen in the sera of the rat. The newly added language of claim 1 reflects such characteristics of the infected rat.

The amendments made herein are fully consistent with and supported by the originally-filed disclosure of this application.

B. Rejection of claims 1, 3, 4, and 6-10 under 35 U.S.C. §103(a)

In the Office Action mailed January 30, 2009 the examiner rejected claims 1, 3, 4, and 6-10 under 35 U.S.C. §103(a) as obvious over Browning et al., *Proc. Nat. Acad. Sci.*, 94:1436-14641, 1997 (hereinafter "Browning"), further in view of U.S. Patent No. 5,625,125 (hereinafter "Bennett").

As noted by the examiner, in the wake of the recent U.S. Supreme Court decision in *KSR International Co. v. Teleflex Inc.*, No. 04-1350, 550 U.S. ___ (April 30, 2007) MPEP §2143 provides examples of rationales to support a conclusion of obviousness. In rejection of claims 1, 3, 4, and 6-10 as obvious over Browning in view of Bennett the examiner identified exemplary rationales A, B and E as applicable:

(A) Combining prior art elements according to known methods to yield predictable results;

(B) Simple substitution of one known element for another to obtain predictable results; and

(E) "Obvious to try."

Applicants respectfully disagree with the examiner's assertion of obviousness in view of the cited combination of Browning in view of Bennett.

As detailed in MPEP §2143, in order to reject a claim based on any of the three above-identified rationales, the examiner must demonstrate predictability of the results. Specifically, under Rationale A, the examiner must demonstrate "a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable;" under Rationale B, the examiner must demonstrate "a finding that one of ordinary skill in the art could have substituted one known element for another, and the results of the substitution would have been predictable;" and under Rationale E, the examiner must demonstrate "a finding that there had been a finite number of identified, predictable potential solutions to the recognized need or problem." Under each exemplary rationale listed in MPEP §2143, it is provided that "[i]f any of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art." Applicants respectfully assert that one of skill in the art could not have predictably arrived at the presently claimed invention from the combination of Browning in view of Bennett, as cited by the examiner.

Applicants have previously asserted in detail that the genomes of rats and mice, while both rodents, are considerably different. In the Response mailed October 2, 2006, applicants illustrated the differences between the mouse and rat genomes, including that the rat genome is significantly larger than the mouse genome and that only about 30% of the rat genome aligns with the mouse. Accordingly, mouse and rat transgenic models are not interchangeably predictive of one another.

The examiner's attention is respectfully drawn to Section I above, where claim 1 has been amended to include the language "…and wherein the rat develops active HIV infection after exposure to HIV, with expression of antibodies or viral antigen in sera thereof." Accordingly, the claims recite a hCD4 transgenic rat that develops an HIV infection following exposure to

HIV. The combination of Browning in view of Bennett does not describe such a transgenic rat, nor is the combination predictive of such transgenic rat.

As described by the examiner, Browning "teaches a method of producing a transgenic mouse comprising a transgene encoding a human CD4 operably linked to a PBMC specific promoter…" (Office Action mailed January 30, 2009, p. 4.) The examiner notes that "Browning et al. does not teach a transgenic rat."

As provided above and as discussed throughout the prosecution of the present application, the characteristics of a transgenic mouse are not necessarily predictive of a transgenic rat. Browning describes the transgenic mouse as susceptible to HIV infection, however such infection is at a cellular level and "…our results indicated that these levels were insufficient to permit sustained productive *in vivo* infection in mice transgenic for human CD4 and CCR5." (Browning, p. 14640.) Browning also provides that "[t]hus, although expression of human CD4 and CCR5 in the transgenic mice overcame the block that prevented entry of HIV-1 into mouse cells, sustained *in vivo* replication of HIV-1 still did not occur." (Browning, p. 14640; emphasis added.) By contrast, the transgenic rats of the present invention do allow for active HIV infection, as recited in amended claim 1.

Bennett is cited as a secondary reference in combination with Browning to demonstrate that "methods of making transgenic rats that successfully express a transgene product was [sic] well established in the art…" (Office Action mailed January 30, 2009, p. 5.)

Applicants do not dispute that transgenic rats were known in the art at the time of the filing of the invention. Bennett expressed a transgenic phospholipase A_2 in both mice and rats. In Bennett, the transgenic animals with high levels of phospholipase in their serum, liver, lung, kidney and skin were generated (Abstract). The animals are useful in testing compounds as inhibitors or antagonists of the expressed phospholipase. The animals in Bennett were not further challenged with a virus, as the presently claimed transgenic rats are.

Additionally, the animals in Bennett expressed observable phenotypes of overexpression of phospholipase A_2, such as severe alopecia, epidermal and adnexal hyperplasia. The hCD4 transgenic rats of the present invention did not demonstrate any observable symptoms of CD4

expression, other than detection of the hCD4 gene in the blood. Transgenic animals expressing one protein are not necessarily predictive of a transgenic animal expressing a different protein.

One of skill in the art, based on the combination of Browning and Bennett would not have predictably expected to successfully achieve a hCD4 transgenic rat that was susceptible to active HIV infection. In fact, where Browning demonstrates that CD4-containing transgenic rats allow cellular HIV infection, but not *in vivo* replication of HIV and where Bennett demonstrates transgenic animals (both rats and mice) that express phospholipase A_2, applicants allege that one of skill in the art would have expected that a CD4-containing transgenic rat would behave similarly to the mouse of Browning, where no active HIV infection was observed in the mouse, or would expect the behavior to be completely unpredictable, based on the knowledge of the differences of the mouse and rat genomes. One of skill in the art would not have the expectation that a hCD4 transgenic rat would predictably be susceptible to active HIV infection.

In *KSR International Co. v. Teleflex Inc.*, No. 04-1350, 550 U.S. ___ (2007), the Supreme Court reaffirmed the principle that a factfinder judging patentability "should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." It is only by the use of impermissible hindsight that the conclusion is drawn that a hCD4 transgenic rat would predictably be susceptible to active HIV infection, based upon the combined showings of Browning and Bennett.

As Browning in light of Bennett does not provide any logical basis for the transgenic rat recited in claims 1, 3, 4, and 6-10, Browning in light of Bennett does not render the claimed invention obvious. Accordingly, withdrawal of the rejection of claims 1, 3, 4, and 6-10 under 35 U.S.C. § 103 (a) as being obvious over Browning in light of Bennett is respectfully requested.

CONCLUSION

Based on the foregoing, all of applicants' pending claims 1, 3, 4, and 6-10 are patentably distinguished over the art, and in form and condition for allowance. The examiner is requested to favorably consider the foregoing and to responsively issue a Notice of Allowance.

The time for responding to the January 30, 2009 Office Action without extension was set at three months, or April 30, 2009. This Response is therefore timely and no fees are believed to be due

for the filing of this paper. However, should any fees be required or an overpayment of fees made, please debit or credit our Deposit Account No. 08-3284, as necessary.

If any issues require further resolution, the examiner is requested to contact the undersigned attorneys at (919) 419-9350 to discuss same.

Respectfully submitted,

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